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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	LAY-014PCTUS	5509

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
11/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,10,12-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4,7,10,12-17,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 22 August 2007 have been entered. Claims 1 – 2, 4, 7, 10, 12 – 17 and 19 are pending.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 22 August 2007 and 22 January 2007 have been entered. Note the amendment after final rejection, filed 22 January 2007, was entered; see Advisory Action mailed 23 February 2007.

Withdrawn Rejections and Objections

3. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection of claims 15 and 19 under 35 USC 112, first paragraph, are withdrawn in light of the amendments which cancel the language the examiner had considered to be new matter.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the limitation "the cells concomitantly administered with the hNT cells" in lines 1 – 2. There is insufficient antecedent basis for this limitation in the claim. The parent claim (claim 15) does not mention additional cells concomitantly administered with hNT cells.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 2, 4, and 17 and rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss (U.S. Patent 5,851,832) in view of Sanberg (1997. Soc. Neurosci Abstr 23(1-2):346, abstract 140.9) and Grabowski (1994. Exp Neurol. 127(1):126-136).

This rejection stands for the reasons previously made of record. Weiss '832 patent teaches methods of treating diseases, including stroke, by administration of the progeny of human neural stem cells. See Weiss column 11 lines 5 – 18; column 3 first paragraph, column 64 lines 13 – 21. While Weiss does not explicitly teach administration of cells to humans who have had stroke, Weiss clearly indicates that stroke is amongst the diseases to be treated by administration of the cells, and provides an example using cerebral artery occlusion (column 64), which was also used by applicant to support enablement of the instant claims (specification, p. 5 lines 17 – 30 for example). Weiss teaches that human stem cells are to be used (see for example column 13 line 45 – 57 and column 40 final paragraph) and teaches how to differentiate the stem cells into neurons (see for example column 18 final paragraph). Weiss teaches administration of progeny of neural stem cells to mice and rats by administering 1 – 3 ul of cells (column 62) at up to 50 x 10^6 cells per ml. This corresponds to up to 150,000 cells per animal. Weiss explicitly teaches using burr holes to provide entry to the skull (column 62 lines 30 – 40), which is in point to claim 2. However Weiss does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites", as recited in claims 1 and 17 and does not

explicitly teach treatment of humans who have experienced stroke at least 3 hours prior to treatment, as recited in claim 1.

Sanberg teaches that hNT cells, transplanted into the brains of rats who had experienced ischemia-inducing surgery a month earlier, are effective to ameliorate behavioral symptoms of stroke. Sanberg teaches that of the doses tested (5,000 – 40,000 cells administered to adult rats), 40,000 cells was the most effective and 5,000 and 10,000 cells were not effective; 20,000 cells per rat was partly effective. The reference therefore is on point to treating stroke with hNT cells; however Sanberg does not explicitly teach administering the cells to humans and does not teach administration of at least 6 million cells, or a plurality of sites as recited in claims 1 and 17. Further Sanberg does not explicitly teach using a burr to enter the brain as recited in claim 2 and does not teach administration of cells 3 months after the stroke as encompassed by claim 4.

Grabowski et al. teach another model of transplantation in which fetal cortex is grafted into the infarcted cortex of rats that having undergone middle cerebral artery occlusion 5-7 days, 3 weeks, or 8 weeks prior. The reference therefore is on point to treatment of stroke by administration of cells into the brains of affected patients. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. However Grabowski does not explicitly teach waiting at least 3 months as recited in claim 4, and does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites" as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Weiss ('832 patent), who indicates that degenerative conditions such as stroke in humans can be treated by administering neural cells, by administering at least 6 million hNT cells, given the teachings of Sanberg. The motivation to do so would be to effectively treat stroke. Sanberg teaches that hNT cells are effective in ameliorating the motor effects of stroke, which is on point to claim 1, and teaches that 40,000 cells are effective. Given that an adult rat weighs approximately 0.3 kg and an adult human weighs approximately 75 kg, it would have been obvious to one of ordinary skill in the art to scale up the dose of cells used by Sanberg accordingly, thereby arriving at a dose of 10 million cells, which meets the limitation "at least 6 million cells" recited in claims 1 and 17. Additionally, it would have been obvious to one of ordinary skill in the art to make the injections at a plurality of brain sites; the motivation to do so

would be to minimize inflammatory trauma at any one site and to deliver the cells to multiple injured brain regions. Finally, the reference by Grabowski provides motivation to one of ordinary skill in the art to wait more than three months, as recited in claim 4, prior to administration of the cells. Grabowski teaches that more of the cells which are administered survive as the delay between stroke and treatment increases, guiding the artisan to select delays even longer than those disclosed in the reference.

Applicant argues, on pp. 7 – 9 of the remarks filed 22 August 2007 that the references which teach treatment of stroke in animals by the middle cerebral artery occlusion method cannot be relied upon in a rejection under 35 USC § 103, as the state of the art was such that it was not possible to extrapolate treatment of humans from the animal models. Applicant relies heavily on certain statements in the reference entitled "Recommendations for Standards Regarding Preclinical Neuroprotective and Restorative Drug Development". Specifically, applicant points to comments which indicate that in some instances success in treatment of animals has not indicated success in treatment of humans.

Applicant's arguments have been fully considered but they are not persuasive. The examiner notes that the Committee did point out certain ways in which the middle cerebral artery occlusion model is imperfect. However, taken as a whole the reference indicates that this model is clearly the best one available for stroke. Specifically, at p. 2756 first paragraph the Committee indicates that "[f]or stroke recovery studies, more limited infarction must be produced, usually by direct surgical occlusion of the proximal MCA (the so called "Trauma" method)." The Committee concludes, in the section entitled "Recommendations" that "[p]utative stroke recovery drugs should be tested in rodent with models of focal cerebral infarction that permit extended recovery." Clearly, while acknowledging certain limitations with MCAO models of stroke, the Committee recognized that this model should be used to test post-stroke therapeutics. This is in fact the same model used by Weiss and by Sanberg. Thus argument that the animal models of stroke, which were used by Weiss, Sanberg, and by applicant, are not sufficiently supportive of treatment in humans is not persuasive.

6. Claims 7, 10, 12 – 17, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sanberg (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of Weiss (U.S. Patent 5,851,832) and Uchida (1995. Exp. Neurol 132:194-208).

This reference stands for the reasons previously made of record. Sanberg (1996) teaches that transplantation of human teratocarcinoma neuronal cells (hNT) to ischemic rats produces recovery of motor function and passive avoidance behavior. The reference is therefore on point to claims 10, drawn to strokes which interfere with movement. Adult rats were subjected to ischemic embolism by middle cerebral artery occlusion were allowed to recover for one month before being tested for asymmetric motor behavior (elevated body swing task, EBST, which is a movement test) and passive avoidance behavior, a cognitive test. Sanberg teaches that one month following transplantation of hNT cells, significant recovery in both the EBST and passive avoidance tasks was observed in groups that received hNT cells as compared to controls. Control animals were reported to show no behavioral recovery. Sanberg concludes that transplantation of hNT cells into the infarcted striatum of rats having stroke improves motor and cognitive deficits associated with such ischemia, and therefore is on point to claims 10, 12, 13, and 15. As the EBST requires sensory input, the reference is on point to claim 14 as well. Additionally, as speech is known to be one of several motor components affected by stroke, the reference is also on point to claim 7. However Sanberg does not teach administration to humans and does not explicitly teach administration of at least 6 million cells and does not explicitly teach sterile compositions.

Weiss ('832 patent) teaches a method for the treatment of neurodegenerative diseases comprising administering to a mammal (such as a human) neural stem cell progeny (which may also be derived from humans) that have been induced to differentiate into neurons and/or glia (column 11, lines 13-17). CNS disorders in the '832 patent encompass numerous afflictions such as neurodegenerative diseases (e.g. Alzheimer's, Parkinson's, Huntington's chorea, ALS), acute brain injury (e.g. stroke, head injury, cerebral palsy), and a large number of CNS dysfunctions (e.g. depression, epilepsy, and schizophrenia) and human demyelinating diseases (e.g. MS) (column 3-4). The patent teaches that acute brain injuries (such as stroke) often result in the loss of neural cells, leading to inappropriate functioning of the affected brain region (column 3, lines 22-24). As disclosed by the '832 patent, treatment of neurodegenerative disease using progeny of human neural stem cells involves first having the patient undergo a CT scan to determine the coordinates of the region to receive the transplant, then using injection cannula to inject the tissue suspension to the correct coordinates (column 42, example 14). It would be an expected property of the injected cell compostion to be sterile if it was used therapeutically in humans. Note Weiss explicitly teaches collection of tissue by sterile technique

(Example 14 among others) and administration of sterile saline (Example 15) as a control; thus it is reasonable that the cells administered in the same experiments are in fact in a sterile composition. Weiss teaches administration of progeny of neural stem cells to mice and rats by administering 1 – 3 ul of cells (column 62) at up to 50 x 10^6 cells per ml. This corresponds to up to 150,000 cells per animal. However Weiss does not teach administration of hNT cells as recited in claims 7, 10, 12 – 15, 17, and 19, and does not teach administration into the cisternae as recited in claim 16.

It would have been obvious to one of ordinary skill in the art to modify the method of Sanberg, who teaches administration of hNT cells to animals with cognitive, sensory, and motor damage from strokes, by following the guidance set forth in Weiss '832 patent and Uchida. Weiss provides guidance as to treatment of human patients and also provides guidance as to selection of the dose. As Weiss teaches administration of 150,000 cells to animals weighing about 0.3 kg, scaling up to humans who weigh about 75 kg would result in administration of 38 million cells to the human patients, which meets the "at least six million" limitation of all independent claims subject to this rejection. Additionally, Uchida provides the artisan with guidance to select intraventricular administration, which is on point to "into the cisternae" as recited in claim 16. The artisan would have been further motivated to inject the cells cisternally, not only because Uchida teaches that implanted neuronal cells can migrate some distance from their implantation site, but also because the an intracisternal injection can be performed without drilling into the skull and is therefore less invasive and would reasonably be expected to result in fewer potential complications. Uchida also provides the motivation to select additional cell types, including fetal non-human cells and neural stem cells which are present in the embryonic neural plate used (see p. 197 second column from Uchida); it is obvious to co-administer two treatments known to be effective for the same purpose. Here, both the hNT cells from Sanberg and the neural stem cells in the composition from Uchida are both known to be suitable for transplantation into brain for therapeutic purposes. Additionally it would have been obvious to one of ordinary skill in the art to treat stroke which "interferes with speech", as this is a type of motor disorder caused by stroke. Given that Sanberg teaches therapeutically treating rats with motor disorders caused by stroke following administration of hNT cells, it would have been obvious to one of ordinary skill in the art to treat human motor deficits, including those related to speech.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
November 20, 2007

RCH

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER